Citation:

Viguerie N, Vidal H, Arner P, Holst C, Verdich C, Avizou S, Astrup A, Saris WH, Macdonald IA, Klimcakova E, Clément K, Martinez A, Hoffstedt J, Sørensen TI, Langin D; Nutrient-Gene Interactions in Human Obesity--Implications for Dietary Guideline (NUGENOB) project. Adipose tissue gene expression in obese subjects during low-fat and high-fat hypocaloric diets. *Diabetologia*. 2005 Jan; 48 (1): 123-131.

PubMed ID: 15624093

Study Design:

Randomized Controlled Trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate the effects of nutrient composition and energy restriction on weight loss and the regulation of adipose tissue gene expression among obese subjects enrolled in the NUGENOB (Nutrient-Gene Interactions in Human Obesity) program.

Inclusion Criteria:

Subjects were participants in the NUGENOB (Nutrient-Gene Interactions in Human Obesity) Study; inclusion criteria for this study were not described.

Exclusion Criteria:

Subjects were participants in the NUGENOB (Nutrient-Gene Interactions in Human Obesity) Study; exclusion criteria for this study were not described.

Description of Study Protocol:

Recruitment

Subjects were participants in the NUGENOB (Nutrient-Gene Interactions in Human Obesity) Study; recruitment for NUGENOB is described elsewhere.

Design

- Subjects were randomly assigned to one of two similarly energy-restricted diets:
  - High-fat, low-carbohydrate diet
  - Low-fat, high-carbohydrate diet

- During the dietary intervention, the subjects either visited or had telephone contact with the dietitian every week to assess compliance and check the content of the diet from food diaries.

Dietary Intake/Dietary Assessment Methodology

- Subjects completed three-day weighed food records for two weekdays and one weekend day before the start of the dietary intervention and at the end of the 10-week diet to assess the habitual diets of the subjects and to assess their compliance with study protocol, respectively
- Subjects also completed one-day weighed food records during the second, fifth, and seventh weeks of the intervention
- All food records were analyses using a food nutrient database.

Blinding Used

None reported.

Intervention

Subjects followed the following diets for 10 weeks:

- High-fat, low-carbohydrate diet
  - Energy intake decreased from 2,271±627kcal per day to 1,567±313kcal per day
  - 42% energy from fat
  - 40% energy from carbohydrate
  - 18% energy from protein
- Low-fat, high-carbohydrate diet
  - Energy intake decreased from 2,301±554kcal per day to 1,617±554kcal per day
  - 24% energy from fat
  - 59% energy from carbohydrate
  - 17% energy from protein.

Statistical Analysis

- A paied Student's T-test was used to test the overall effect of energy restriction
- Gene expression data were log transformed prior to analysis
- General linear model univariate analysis was used to study the differential effect of the diet with adjustment for baseline mRNA level (week zero) to increase precision and statistical power. The model included adjustment for clinical centers. To control for changes in other parameters that could hide the differential effect of these diets (e.g., changes in BMI and fat mass), these variables were entered independently into the model
- Hierarchical cluster analysis was performed using Euclidean distances as an estimate of similarity between two genes and Ward's method to join groups of genes
- A P-value ≤ 0.05 was considered to be statistically significant.

Data Collection Summary:

Timing of Measurements

- Subjects consumed the study diets for 10-weeks
- Subjects completed three-day weighed food records (two weekdays and one weekend day) before the start of the dietary intervention and at the end of the 10-week diet to assess the

habitual diets of the subjects and to assess their compliance with study protocol, respectively
- Subjects also completed one-day weighed food records during the second, fifth, and seventh weeks of the intervention
- Subjects were weighed when they visited the centers on every second week of the study
- Gene expression was measured before and after the dietary intervention.

Dependent Variables

- Weight was measured at the clinic
- Fat mass and fat-free mass (FFM) were measures using multifrequency bioimpedance
- Plasma leptin and NEFA levels were determined using the human leptin RIA kit and the NEFA-C kit
- Gene expression (quantitation of mRNA) was measured using biopsy samples of abdominal adipose tissue following an overnight fast. Samples were analyzed using PCR, and mRNA levels were determined for 38 genes.

Independent Variables

Dietary intake was measured using weighed food records.

Control Variables

This was a multi-center trial, so analyses were adjusted for clinical center.

Description of Actual Data Sample:

- *Initial N:* 771 females (total patients who participated in the NUGENOB study)
- *Final N:* 50 females (chosen at random from the total number who participants in the NUGENOB study)
  - N=25 for the high-fat diet
  - N=25 for the low-fat diet
- *Age:* 21 to 49 years; mean age was not reported
- *Ethnicity:* Not reported
- *Other relevant demographics:* None reported
- *Anthropometrics:* Mean BMI was 36.2±0.7kg/m^2 at baseline; other anthropometrics are reported in the Summary of Results section
- *Location:* Europe.

Summary of Results:

Anthropometric and Metabolic Parameters of Subjects Following High- and Low-Fat Hypocaloric Diets

Parameters	High-Fat Diet			Low-Fat Diet			Differential Effect of Diet
	Before	After 10 Weeks	P-value	Before	After 10 Weeks	P-value	P-value

Weight (kg)	99.4±2.7	92.7±2.8	<0.0001	100.3±3.9	93.5±4.1	<0.0001	NS
BMI (kg/m^2)	36.1±0.9	33.6±0.9	<0.0001	36.3±1.2	33.8±1.3	<0.0001	NS
Percent fat	43.4±1.2	40.4±1.3	<0.0001	43.8±1.6	39.2±1.4	<0.0001	NS
Fat mass (kg)	43.5±2.0	37.7±2.0	<0.0001	43.7±2.7	37.2±2.6	<0.0001	NS
Fat-free mass (kg)	56.2±1.6	55.0±1.7	0.028	56.6±2.4	56.3±2.2	NS	NS
Resting Energy Expenditure (REE; kcal per day)	1,869±65	1,786±69	0.031	1,914±93	1,815±100	0.06	NS
NEFA (µmol/L)	491±28	504±32	NS	536±27	429±27	0.007	0.051
Triglycerides (µmol/L)	1,477±274	1,162±135	NS	1,021±110	988±100	NS	NS
HDL cholesterol (mmol/L)	1.1±0.1	1.1±0.1	NS	1.1±0.1	1.0±0.1	0.009	NS
LDL cholesterol (mmol/L)	3.43±0.2	3.2±0.2	NS	3.3±0.1	2.9±0.1	0.002	NS
Glucose (mmol/L)	5.6±0.1	5.4±0.1	0.015	5.5±0.3	5.4±0.4	NS	NS
Insulin (µU/ml)	12.5±1.2	10.9±1.2	0.057	11.3±1.6	10.3±2.0	NS	NS
Insulin Sensitivity (QUICKI)	0.47±0.01	0.5±0.1	<0.0001	0.5±0.01	0.5±0.01	<0.0001	NS
Leptin (ng/mL)	30.9±2.8	21.2±2.5	<0.0001	29.3±2.7	19.5±2.5	<0.0001	NS

- Both diets resulted in significant decreases in body weight, and there were no differences in weight loss between the two diet types
- Both diets resulted in significant decreases in BMI, percent fat, fat mass, FFM, resting energy expenditure (REE), insulin sensitivity and leptin
- The high-fat diet also resulted in significant decreases in glucose and insulin, while the low-fat diet resulted in significant decreases in REE, NEFA, and both HDL and LDL cholesterol
- NEFA decreased significantly in the low-fat groups compared to the high-fat group.

Gene Expression Data

- None of the 38 genes tested were identified as being differentially regulated by the different

diets tested in this study
- The overall effect of the 10-week energy restriction impacted 10 genes significantly:
  - Lower levels were seen for: Osteonectin, phosphodiesterase 3B, receptor A for natiuretic peptide, fatty-acid translocase/CD36, uncoupling protein 2, lipoprotein lipase, leptin, hormone-sensitive lipase and peroxisome proliferator-activated receptor γ 2 (PPARγ2)
  - Higher levels were seen for: Transcript encoding PPARγ co-activator 1α (PGC-1α).

Author Conclusion:

- Both hypocaloric high- and low-fat diets effectively resulted in significant weight loss over a 10-week period
- Macronutrient composition of the diet, energy restriction and weight loss had minimal effects on adipose tissue gene expression.

Reviewer Comments:

- *This study only tested women, so the effects in men are unknown*
- *The short length of this study, 10 weeks, makes it unclear whether the different diets would have differential impacts on weight if followed for a longer period of time*
- *This study did not control for physical activity, and other parameters that may have affected body weight*
- *Subject characteristics were not adequately described in this study (inclusion/exclusion criteria, mean age, race, ethnicity or other key demographics).*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes

1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	No
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	No
2.2.	Were criteria applied equally to all study groups?	???
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes

4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes

7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	No
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes